THE LANCET
Respiratory Medicine

Supplementary appendix 1

This appendix formed part of the original submission. We post it as supplied by the authors.

Supplement to: Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020; published online October 16. https://doi.org/10.1016/S2213-2600(20)30404-5.

Cytokine Elevation in Severe and Critical COVID-19: A Rapid Systematic Review, Meta-Analysis, and Comparison to Other Inflammatory Syndromes

Leisman and Ronner, et al.

Supplemental Material

TABLE OF CONTENTS

Supplemental Methods

i. Complete search strategies Pg. 1
ii. Inclusion/Exclusion criteria – COVID-19 Pg. 2
iii. Inclusion/Exclusion criteria – Comparator Disorders Pg. 3
iv. Search Strategy Rationale Pg. 4
v. Data abstraction – detailed methods Pg. 5
vi. Statistical analysis – detailed methods Pg. 6

Supplemental Tables

sTable-1: Criteria for severe and critical COVID-19 Pg. 8
sTable-2: Criteria for cytokine release syndrome grading Pg. 9
sTable-3: Studies where data were requested from corresponding authors Pg. 10
sTable-4: COVID-19 studies included in final meta-analysis Pg. 11
sTable-5: Non-COVID studies included in final meta-analysis Pg. 12
sTable-6: Pooled mean IL-6 estimates; inverse-variance weighting and without log transformation sensitivity analyses Pg. 13
sTable-7: Analysis of IL-6 in COVID-19 vs. comparator disorders, with ARDS pooled Pg. 14
sTable-8: Frequency of studies reporting inflammatory cytokines and biomarkers of interest Pg. 15
sTable-9: Tabulated pooled means and differences for other cytokines vs. all-COVID Pg. 16
sTable-10: Pooled mean IL-6 estimates distinguishing severe from critical COVID-19; inverse-variance weighting and without log transformation sensitivity analyses Pg. 17
sTable 11: Tabulated pooled means and differences for other cytokines vs. critical-COVID subgroup Pg. 18
sTable 12: Timing of IL-6 measurement in included COVID-19 studies Pg. 19
sTable 13: Sensitivity analyses of peak IL-6 in COVID-19 vs. comparator disorders Pg. 20

References Pg. 21

Supplemental Methods (i): Complete Search Strategies

Embase (Ovid)

1. Coronavirus infection/
2. (2019-nCoV or 2019nCoV or COVID-19 or SARS-CoV-2 or novel coronavirus).mp.
3. 1 or 2
4. exp cytokine/
5. (Cytokine* or Interleukin* or IL-6 or IL6 or Tumor necrosis factor or TNF* or "T cells" or "B cells").mp.
6. 4 or 5
7. 3 and 6
8. limit 7 to dc=20191101-20200414

Medline (Ovid)

1. Coronavirus Infections/
2. (2019-nCoV or 2019nCoV or COVID-19 or SARS-CoV-2 or novel coronavirus).mp.
3. 1 or 2
4. exp Cytokines/
5. (Cytokine* or Interleukin* or IL-6 or IL6 or Tumor necrosis factor or TNF* or "T cells" or "B cells").mp.
6. 4 or 5
7. 3 and 6
8. limit 7 to dt=20191101-20200414

MedrXiv

Due to the character limit on MedrXiv's search functionality, the MedrXiv search was executed in two successive rounds.

Search 1

(2019-nCoV OR 2019nCoV OR COVID-19 OR SARS-CoV-2 OR novel coronavirus) AND (cytokine or Interleukin)

Search 2

(2019-nCoV OR 2019nCoV OR COVID-19 OR SARS-CoV-2 OR novel coronavirus) AND (IL6 OR Tumor necrosis factor OR TNFα)

Supplemental Methods (ii): Inclusion/Exclusion Criteria – COVID-19

Our analyses included original research studies that reported IL-6 levels for hospitalized patients with either “severe” or “critical” laboratory-confirmed COVID-19. Severe COVID-19 was identified by either World Health Organization (WHO) criteria[1] or National Health Commission of China (NHCC) criteria[2] (see **Supplemental Table-1**). Broadly, this classification includes COVID-19 patients with respiratory distress who do not receive invasive mechanical ventilation. We classified patients with “critical” COVID-19 as those who met either NHCC criteria,[2] or WHO criteria for COVID-induced ARDS (which align with the Berlin Criteria for ARDS),[1,3] or who were admitted to an intensive care unit (ICU) and received invasive mechanical ventilation if severity was not otherwise specified. Case-series including only deceased subjects were also treated as critical COVID-19. We excluded studies with < 20 subjects, non-English language, or if measures of central tendency and distribution were not reported in tabular or graphical form and were not available from the corresponding author.

Supplemental Methods (iii): Inclusion/Exclusion Criteria – Comparator Disorders

Data for the comparator disorders were obtained from pre-specified landmark trials. For ARDS, we used data reported from the SAILS trial and from the pooled analysis of the ALVEOLI, ARMA, and FACCT trials.[4,5] We chose these trials because they involved large numbers of patients and robust biomarker data within the distinct, repeatedly-validated hyper-inflammatory and hypo-inflammatory ARDS sub-phenotypes.[6] We reasoned that this distinction would facilitate a more nuanced comparison to ARDS in COVID-19. For sepsis, data were obtained from the ACCESS, PROWESS, ProCESS, and GenIMS studies, respectively.[7] These four large cohorts previously reported a large quantity of cytokine and biomarker data and reflect a broad spectrum of disease severity.[7] For CRS, we obtained data from studies in a spectrum of hematologic malignancies treated with CAR T cell therapy.[8-11] We restricted the data to patients with ≥grade-3 CRS, which generally involves organ dysfunction that prompts the administration of tocilizumab (grading criteria detailed in **Supplemental Table-2)**. One protocol deviation occurred in obtaining CRS control data - a pre-specified trial (Turtle *et al.*) reported data for ≥grade-2 in aggregate only.[12] After approaching the corresponding author for granular data, we were informed that only two patients had ≥grade-3 CRS. However, this author provided the data for all ≥grade-3 CRS patients in another larger study that included these subjects (Hay *et al.*), of which we were previously unaware.[9] These data were included as part of the CRS control group in the final analysis instead of the pre-specified study by Turtle *et al.*

Supplemental Methods (iv): Search Strategy and Study Selection

This study employed a rapid-review methodology as follows.[13,14] A medical librarian (RP) with expertise in systematic-review search methodology designed and executed a comprehensive search strategy (**Supplemental Methods**). The search, which included all relevant subject headings and keywords, was run in the Embase and MEDLINE databases and limited to articles published between November 1, 2019 – April 14, 2020. Additional searching was conducted in the preprint repository, *MedrXiv*, for relevant preprints.

Results from all sources were imported into the Covidence review management tool (*Covidence Organization, Melbourne, Australia*). Results were de-duplicated and the titles and abstracts of each record were screened by one reviewer (LR or DL). The entirety of the remaining articles were then reviewed to identify studies for analysis. Disagreements were resolved by discussion.

Supplemental Methods (v): Data Abstraction – detailed methods

Two reviewers (LR and DL) abstracted data from all studies that met inclusion criteria using a standardized data-collection tool. Since some have argued cytokine elevation is a “late” finding in COVID-19, we abstracted the peak IL-6 value for studies the reported multiple IL-6 levels in an effort to be conservative. All studies reported a measure of central tendency (mean or median) and spread (standard deviation, standard error, interquartile range (IQR), or range) for IL-6 levels. For studies that did not report these statistics (e.g., IL-6 reported as figures), or that did not report them in the specific population of interest (e.g., in an overall study population that included non-severe COVID-19), the data were requested from the corresponding authors. All such authors were contacted at least 3-times over a 3-week period. If the authors did not provide the necessary data but the data could be estimated from the reported results (e.g., from a scatterplot figure), the necessary statistics were derived in this manner. However, if the corresponding author did not provide the data and the statistics could not be determined from the reporting format, the study was excluded. Measurement units were standardized across studies to ensure fair comparison. All cytokines were reported in pg/mL. In the case of d-dimer specifically, results were standardized to μg/mL. However in two studies (Gao Y. et al. and Zhang H. et al.), d-dimer was reported as “μg/L” but correcting to μg/mL resulted in implausibly low values. It was therefore assumed that authors intended to report μg/mL or mg/L and the reported values were included without correction factor.

Supplemental Methods (vi): Statistical Analysis – detailed methods

Means and standard deviations were left unchanged where reported. Where medians and interquartile range or range were reported, we adhered to Cochrane recommendations, estimating the mean using the method described by Wan *et al.*,[15] and the standard deviation using the Cochrane handbook method.[16] Since we expected many markers to display a beta distribution, we evaluated each response variable graphically prior to analysis and applied a log-transformation if normality assumptions were violated. We include analysis of the untransformed data as sensitivity analyses. Additionally, after data-collection, we found that central tendency was positively correlated with the variance (i.e., violated the homoscedasticity assumption) for many biomarkers, including IL-6. Since the common practice of inverse-variance weighting would bias the estimates downward in this situation,[17] we instead weighted studies by the square-root of the sample size in the primary analysis. However, we also performed standard inverse-variance weighting as sensitivity analysis. An important point is that while the method by Wan *et al*. for estimating means from median and quartiles been validated for beta distributed data, it may nevertheless underestimate means in this type of data.[15] However, the degree of underestimation positively correlates with the degree of right-skew,[15] and as we observed, the degree of right-skew was positively correlated with central tendency for most cytokines. Therefore, this effect would be expected to be greater for datasets with higher cytokine levels. That is, misestimation may contribute to under-, rather than over-estimation, of the differences between COVID-19 and the comparator disorders.

After computing study-weights, pooled means were calculated from a generalized linear model with "disorder" as a class variable with the levels, COVID-19, CRS, hypo-inflammatory ARDS, hyper-inflammatory ARDS, and sepsis by estimating the least-squares means at each level. We constructed 95% confidence-limits and p-values for the difference between each of other disorders vs. COVID-19 using the Dunnett correction for multiple comparisons. We had originally hoped to analyze the data

using a mixed-effects model where each study was entered as level of a random-effect. However, it became apparent after data-collection that this was not possible, because doing so requires a unique intercept be specified for each individual study. Given that all studies report data for only one of the syndromes of interest, (i.e., COVID-19, ARDS, sepsis, or CRS), specifying a unique intercept for each study would preclude between-disorder comparisons. For this reason, we opted for a simpler model with "disorder" entered as a fixed-effect.

To facilitate interpretation for variables that had been log-transformed, we back-transformed the estimated means and confidence-limits for reporting purposes. We calculated I^2 statistics to assess between-study heterogeneity within disorders.

For the secondary analysis, the procedures above were repeated with the disorder variable including separate levels for severe vs. critical COVID-19. Unlike "critical" COVID-19, "severe" COVID-19 may included a less severely ill population relative to non-COVID ARDS. Therefore we selected critical COVID-19 as the reference level for statistical hypothesis testing. Studies that did not distinguish severe from critical patients were excluded from these analyses.

In additional set of sensitivity analysis, IL-6 levels were calculated among only COVID-19 studies that reported a peak IL-6 level. For these analyses, "peak" was considered either the highest reported IL-6, or drawn within 48 hours of death for the case-fatality series. These comparisons were then made distinguishing "severe" from "critical" COVID-19 as above.

Supplemental Table 1: Criteria for "Severe" and "Critical" COVID-19 in this Analysis

Classification System	**Clinical Criteria**
National Health Commission of China	
"Severe" COVID-19	Confirmed SARS-CoV-2 infection + ≥1 of the following conditions met: 1) respiratory rate > 30 2) severe dyspnea 3) SpO2 ≤93% at rest 4) a PaO2/FiO2 ratio <300 5) new lung infiltrates in >50% of the lung field within 24-48 hours
"Critical" COVID-19	"Severe" COVID-19 in addition to ≥1 of the following conditions met: 1) Respiratory failure and requiring mechanical ventilation 2) Shock 3) Other organ failure requiring intensive care unit-level care.
World Health Organization	
Severe COVID-19 Pneumonia *("Severe" COVID-19 in this study)*	Confirmed SARS-CoV-2 infection + ≥1 of the following conditions met: 1) respiratory rate > 30 2) severe dyspnea 3) SpO2 ≤93% on room-air
ARDS in COVID-19 *("Critical" COVID-19 in this study)*	"Severe" COVID-19 in addition to *all* of the following conditions met: 1) Chest imaging showing bilateral opacities not fully explained by volume overload, lobar or lung collapse, or nodules. 2) Respiratory failure not fully explained by cardiac failure or fluid overload and hydrostatic causes excluded by objective assessment (e.g, echocardiography) or presence of edema in absence of risk factors. 3) PaO2/FiO2 ratio <300

Abbreviations: ARDS – acute respiratory distress syndrome; SpO2 – oxygen saturation; PaO2 – arterial partial pressure of oxygen; FiO2 – fraction of inspired oxygen.

Supplemental Table 2: CRS grading, Penn/CHOP vs. Lee criteria†

	Penn/CHOP	*Lee*	*Included in Meta-Analysis?*
Grade 1	Mild reaction: treated with supportive care such as antipyretics, antiemetics	Symptoms are not life-threatening and require symptomatic treatment only, e.g. fever, nausea, fatigue, headache, myalgias, malaise	No
Grade 2	Moderate reaction: some signs of organ dysfunction (e.g., grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including fevers with associated neutropenia, need for IV therapies (not including fluid resuscitation for hypotension)	Symptoms require and respond to moderate intervention. Oxygen requirement < 40% or hypotension responsive to fluids or low-dose pressors or grade 2 organ toxicity	No
Grade 3	More severe reaction: hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias; includes hypotension treated with intravenous fluids (defined as multiple fluid boluses for blood pressure support) or low-dose vasopressors, coagulopathy requiring fresh frozen plasma or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP)	Symptoms require and respond to aggressive intervention. Oxygen requirement ≥ 40% or hypotension requiring high-dose or multiple pressors or grade 3 organ toxicity or grade 4 transaminitis	**Yes**
Grade 4	Life-threatening complications such as hypotension requiring high-dose vasopressors; hypoxia requiring mechanical ventilation	Life-threatening symptoms. Requirements for ventilator support or grade 4 oxygen toxicity (excluding transaminitis)	**Yes**

**Abbreviations: CHOP = Children's Hospital of Philadelphia, CRS = cytokine release syndrome, LFTs = liver function tests, CPAP = continuous positive airway pressure, BiPAP = bilevel positive airway pressure; all "grade X" organ toxicities refer to CTCAE grading.*

†Table adapted from Porter D. et al. "Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenleucel," J. Hematol Oncol. 2018.

Supplemental Table 3: Studies where clarifying data was requested (6 of 28 COVID, 1 control); outcome of request

Study	*Reason for request*	*Article stated "Data available upon request"*	*Corresponding Author*	*Responded to Request*	*Provided data?*	*Used in analysis*
Diao B. et al.	Difficult to estimate mean(SD) or median(IQR) from figures; not otherwise reported	Yes	Chen, Yongwen	Yes	Yes	Yes
Turtle C. et al.	Data for patients with CRS grade 2-5 binned, inclusion criteria specified grade 3+	Not specified	Turtle, Cameron	Yes	Yes	Yes
Yang Y. et al.	Unable to estimate mean(SD) or median(IQR) from figures, not otherwise reported	Yes	Liu, Yingxia	Yes	Yes	Yes
Liu T. et al.	Difficult to estimate mean(SD) or median(IQR) from figures, not otherwise reported	**Yes**	Zhang, Liling	**No**	No	**Yes**
Tan L. at al.	Unable to estimate mean(SD) or median(IQR) from figures, not otherwise reported	**Yes**	Miao, Hongming	**Yes**	**No**	No
Zhou H. et al.	Unable to estimate mean(SD) or median(IQR) from figures, not otherwise reported	**Yes**	Hu, Desheng	**No**	**No**	No
Gong J. et al.	Difficult to estimate mean(SD) or median(IQR) from figures, not otherwise reported	**Yes**	Fuer, Lu	**No**	**No**	No

Supplemental table 4 – COVID-19 studies included in final meta-analysis

Study	*Year*	*Source*	*Inclusion Criteria*	*Exclusion Criteria*	*Total N*	*Severe N*	*Severe definition*	*Critical N*	*Critical definition (comments)*
Cai Q.	2020	Epidemiology and Genetics	Hospitalized, PNA, lab-confirmed SCV2	none	298	58	CT scan w/ >30% lung involvement	-	-
Chen G.	2020	J Clin Invest	Hospitalized, PNA, lab-confirmed SCV2	none	21	13	NHCC guidelines v6	-	-
Chen J	2020	MedRxiv	ICU pts who died with pathogenic evidence, +PCR, or homologous gene sequencing c/w coronavirus	none	101	-	-	101	Admitted to ICU, died
Chen X.	2020	MedRxiv	Hospitalized, PNA, lab-confirmed SCV2	none	48	10	NHCC guidelines v6	17	Resp. failure requiring mech. vent.; shock; multiple organ failure requiring ICU
Diao B.	2020	Front Immunol	Confirmed SCV2, ICU admission	none	522	-	-	43	HFNC or higher-level O2 support required
Fu S.	2020	MedRxiv	Hospitalized, PNA, lab-confirmed SCV2	none	50	50	Not defined	-	-
Gao Y.	2020	J Med Virol	Hospitalized, PNA, lab-confirmed SCV2	none	43	15	Not defined	-	-
Gritti	2020	MedRxiv	'Confirmed' SCV2 (no info on diagnostic modality), w/ ARDS requiring NIV, receiving siltuximab	none	21	21	Requiring NIMV	-	-
Herold	2020	MedRxiv	Hospitalized, PNA, lab-confirmed SCV2	none	40		-	13	Requiring endotracheal intubation
Huang C.	2020	The Lancet	Hospitalized, lab-confirmed SCV2	none	41		-	13	Requiring HFNC or higher O2 support
Huang Y.	2020	MedRxiv	Hospitalized, PNA, lab-confirmed SCV2, died	none	36		-	36	Died
Liu J.	2020	MedRxiv	Hospitalized, PNA, lab-confirmed SCV2	none	40	13	Not defined	-	-
Liu T.	2020	MedRxiv	Hospitalized, lab-confirmed SCV2	none	80	69	NHCC guidelines v5	-	-
Qin C.	2020	Clin Infec Dis	Hospitalized, PNA, lab-confirmed SCV2	none	452	286	WHO interim guidance for NCP	-	-
Ruan Q.	2020	Intensive Care Med	Hospitalized, lab-confirmed SCV2	none	150		-	68	Died
Shi Y.	2020	MedRxiv	Hospitalized, lab-confirmed SCV2	none	56	25	NHCC guidelines v6	-	-
Wan S.	2020	MedRxiv	Hospitalized, lab-confirmed SCV2	none	123	21	WHO interim guidance for NCP	-	-
Wang Z.	2020	Clin Infec Dis	Hospitalized, lab-confirmed SCV2	none	43	7	Admission SpO2 < 90%	-	-
Wu C.	2020	JAMA Int Med	Hospitalized, PNA, lab-confirmed SCV2	none	201	-	WHO ARDS Criteria	-	*(137 patients contributing to all-COVID analysis)*
Xu Y.	2020	MedRxiv	Hospitalized, PNA, lab-confirmed SCV2	†	69	25	WHO interim guidance for NCP	-	-
Yang Y.	2020	J Allergy and Clin Immunol	Hospitalized, lab-confirmed SCV2	none	50	25	NHCC guidelines (version unspecified)	11	NHCC guidelines (version unspecified)
Zhang B.	2020	MedRxiv	Lab-confirmed SCV2, died	none	82	-	-	82 /11 ‡	died
Zhang H.	2020	MedRxiv	Hospitalized, lab-confirmed SCV2	none	43	14	WHO interim guidance for NCP	-	-
Zhang, B.	2020	MedRxiv	Hospitalized, lab-confirmed SCV2	none	222	-	-	-	*(91 patients contributing to all-COVID analysis)*
Zhou F.	2020	The Lancet	Hospitalized, PNA, lab-confirmed SCV2	none	191	-	-	54	Died

**Abbreviations: PNA = pneumonia, SCV2 = SARS-CoV-2, WHO = World health Organization, NHCC = National Health Commission China, CT = computed tomography, HFNC = nigh-flow nasal cannula, I = intensive care unit, NIMV = non-invasive mechanical ventilation, NCP = Novel Coronavirus Pneumonia,*

†Cardiovascular disease, hypertension, "chronic" gastrointestinal or renal disease, chronic obstructive pulmonary disease, hepatitis B virus carrier, depression, autoimmune disease, "other diseases"

‡ The study included 82 fatal COVID-19 cases. While secondary biomarkers were available for all patients, IL-6 was reported for only 11 of the 82 patients.

Supplemental table 5 – Non-COVID studies included in final meta-analysis

ARDS

Study	Year	Source	Inclusion/ Exclusion Criteria	Total N	Hypo-inflammatory N	Hyper-inflammatory N
Sinha et al.	2020	*Lancet: Resp Med*	Enrollment in FACCT, ARMA, or ALVEOLI trials + available biomarker data	2022	1431	591
FACCT	2006	*N Eng J Med*	Intubated patients receiving positive pressure ventilation + development of bilateral infiltrates + PaO2/FiO2 ratio <300 + no evidence of left hypertension <48h before enrollment.	--	--	--
ARMA	2000	*N Eng J Med*	Intubated patients receiving positive pressure ventilation + development of bilateral infiltrates + PaO2/FiO2 ratio <300 + PCWP < 19 mmHg <36h before enrollment	--	--	--
ALVEOLI	2008	*JAMA*	Intubated patients with bilateral chest infiltrates and PaO2/FiO2 ratio <300 unlikely to be due to left atrial hypertension.		--	--
Sinha et al. (SAILS)	2018	*Intensive Care Med*	Available biomarker data and enrollment in the SAILS trial, which required: ≥2 SIRS + intubation and positive pressure ventilation + bilateral infiltrates + PaO2/FiO2 ratio <300 + either no evidence of left atrial hypertension or PCWP < 19 mmHg, developing < 48h prior to enrollment	745	468	277

Sepsis

Study	Year	Source	Inclusion/Exclusion Criteria	Total N
GenIMS	2007	*Arch Intern Med*	Emergency Department patients with community acquired pneumonia + ≥2 SIRS + ≥1 new organ dysfunction	583
ACCESS	2013	*JAMA*	Suspected or confirmed infection + ≥3 SIRS + ≥1 new organ dysfunction with onset <12h before enrollment + APACHE-II score ≥21 but < 38.	1706
PROWESS	2001	*N Eng J Med*	Suspected or confirmed infection + ≥3 SIRS + ≥1 new organ dysfunction with onset < 24h before enrollment	1690
ProCESS	2014	*N Eng J Med*	Emergency Department patients with suspected or confirmed infection + ≥2 SIRS + refractory hypotension or Lactate>4	1341

CAR T-induced Cytokine Release Syndrome

Study	Year	Source	Patients	Study N	Severe or grade 3+ CRS	CRS grading scale or definition of severity
CART19	2014	*N Eng J Med*	r/r B-ALL, children & young adults	30	8	Requiring respiratory support (NC or greater), vasopressor support
ELIANA	2018	*N Eng J Med*	r/r B-ALL, children & young adults	75	35	Penn/CHOP scale†
ZUMA-1	2017	*N Eng J Med*	Large B-cell lymphoma (incl. DLBCL, large mediastinal primary, transformed follicular), adults	111	13	Lee criteria‡
Hay et al.	2017	*Blood*	r/r B-ALL, CLL, or NHL, adults	133	16	Lee criteria

Abbreviations: NC: nasal cannula, B-ALL: B-cell acute lymphoblastic leukemia, DLBCL: diffuse large B-cell lymphoma, CLL: chronic lymphocytic leukemia, NHL: non-hodgkin lymphoma.
† Grade 3: CTCAE grade 4 LFTs or grade 3 creatinine, hypotension requiring IVF or low-dose pressors, hypoxia requiring supplemental O2 (nasal canula, high flow, CPAP, or BiPAP), coagulopathy requiring FFP or cryoprecipitate or fibrinogen concentrate.
Grade 4: hypotension requiring high-dose vasopressors, hypoxia requiring mechanical ventilation
‡ Grade 3: O2 requirements ≥ 40% fiO2 or hypotension requiring high-dose or multiple pressors or CTCAE grade 3 organ toxicity or grade 4 transamenemia
Grade 4: requirement for ventilator support or CTCAE grade 4 organ toxicity (excluding transamenemia)

Supplemental Table 6: primary and sensitivity analyses for IL-6 in pooled COVID-19 and comparison syndromes

	sqrt(N)-weighted analysis (primary)			***Inverse-variance weighted analysis***			***Non-transformed analysis***		
	Mean *pg/mL* *(95%CI)*	**Difference vs. COVID (95% CI)**	**p**	**Mean *pg/mL* (95%CI)**	**Difference vs. COVID (95% CI)**	**p**	**mean *pg/mL* (95%CI)**	**Difference vs. COVID (95% CI)**	**p**
COVID-19	36.7 (21.6-62.3)	***ref***	*ref*	22.2 (14.4-34.1)	***ref***	*ref*	15.3 (14.3-16.3)	***ref***	*ref*
Hypo-inflammatory ARDS	198.6 (81.1-486.4)	**161.9 (15.6-717.3)**	0.0085	193.7 (66.5-564.2)	**1,71.5 (23.8-831.6)**	0.0020	172.1 (167.9-176.3)	**156.8 (151.7-161.9)**	<0.0001
Hyper-inflammatory ARDS	1,558.2 (529.5-4,585.3)	**1,521.5 (296.9-7,240.5)**	<0.0001	1,558.2 (337.4-7,197.6)	**15,36.0 (296.1-19,881.7)**	<0.0001	1,552.8 (1,538.5-1,567.1)	**1,537.5 (1,519.1-1,555.8)**	<0.0001
Sepsis	983.6 (552.2-1,751.8)	**946.9 (323.6-2,648.2)**	<0.0001	796.2 (358.8-1,766.2)	**7,74.0 (373.3-4,183.8)**	<0.0001	405.4 (400.4-410.4)	**390.1 (384.0-396.3)**	<0.0001
CAR T CRS	3,110.5 (632.3-15,302.9)	**3,074.0 (324.7-26,735.0)**	<0.0001	859.6 (129.3-5,714.1)	**837.4 (79.9-17,269.2)**	0.0005	202.6 (198.6-206.6)	**187.3 (182.6-191.9)**	<.00001
Model Fit			***R^2 = 0.73***			***R^2 = 0.71***			***R^2 = 0.35***

All p-values and confidence-intervals are corrected for multiple comparisons.

**Abbreviations: sqrt(N) = square root of sample size, COVID = coronavirus disease 19, hypo-ARDS = hypo-inflammatory acute respiratory distress syndrome, hyper-ARDS = hyperinflammatory acute respiratory distress syndrome, CAR T = chimeric antigen receptor T cell, CRS = cytokine release syndrome*

Supplemental Table 7: Analysis of IL-6 in COVID-19 vs. comparator disorders, with ARDS pooled

	All COVID			***Severe and Critical COVID subgroups***		
	Mean *pg/mL (95%CI)*	**Difference vs. Critical COVID-19 (95%CI)**	**p**	**Mean *pg/mL (95%CI)***	**Difference vs. Critical COVID-19 (95%CI)**	**p**
All COVID-19	36.7 (20.5 – 65.5)	***ref***	***ref***	-	**-**	-
Severe COVID-19	-	**-**	-	39.9 (15.9 – 100.1)	**-9.9 (-42.3 – 164.6)**	0.9909
Critical COVID-19	-	**-**	-	49.8 (18.9 – 130.9)	***ref***	***ref***
Pooled ARDS	460.1 (216.3 – 978.7)	**423.4 (106.9 – 1,438.0)**	<0.0001	460.1 (209.0 -1,012.9)	**410.2 (45.7 – 2,166.9)**	0.0035
Sepsis	983.6 (522.7 – 1850.6)	**946.9 (307.6 – 2,773.0)**	<0.0001	983.6 (508.0 – 1,904.5)	**933.5 (175.0 – 4,251.2)**	<0.0001
CAR T CRS	3,110.5 (543.4 – 17,804.0)	**3,073.8 (291.2 – 29470.4)**	<0.0001	3,110.5 (502.0 – 19,273.1)	**3,059.8 (181.0 – 41,862.1)**	0.0010
Model Fit			***R^2 = 0.66***			***R^2 = 0.63***

All p-values and confidence-intervals are corrected for multiple comparisons.

**Abbreviations: COVID-19 = coronavirus disease 19, ARDS = acute respiratory distress syndrome, CAR T = chimeric antigen receptor T cell, CRS = cytokine release syndrome*

Supplemental Table 8 – Frequency of studies reporting inflammatory cytokines and biomarkers of interest

Disorder	IL-6	TNFa	IFNy	IL-10	IL-8	sIL-2R	IL-2	IL-4	IL-1b	Ferritin	CRP	LDH	d-dimer	PCT	ESR	Fibrinogen	Albumin	tBili	Abs. Lymph.	% Lymph.	Platelets
Severe CoViD-19	15/15, (100%)	8/15, (53%)	5/15, (33%)	9/15, (60%)	2/15, (13%)	3/15, (20%)	6/15, (40%)	7/15, (47%)	2/15, (13%)	3/15, (20%)	11/15, (73%)	8/15, (53%)	7/15, (47%)	9/15, (60%)	5/15, (33%)	2/15, (13%)	2/15, (13%)	3/15, (20%)	11/15, (73%)	3/15, (20%)	5/15, (33%)
Critical CoViD-19	10/10, (100%)	1/10, (10%)	3/10, (30%)	3/10, (30%)	1/10, (10%)	1/10, (10%)	2/10, (20%)	2/10, (20%)	1/10, (10%)	3/10, (30%)	4/10, (40%)	8/10, (80%)	5/10, (50%)	7/10, (70%)	0/10, (0%)	1/10, (10%)	4/10, (40%)	6/10, (60%)	8/10, (80%)	1/10, (10%)	6/10, (60%)
All CoViD-19	25/25, (100%)	10/25, (40%)	7/25, (28%)	12/25, (48%)	3/25, (12%)	3/25, (12%)	9/25, (36%)	10/25, (40%)	3/25, (12%)	7/25, (28%)	15/25, (60%)	16/25, (64%)	13/25, (52%)	14/25, (56%)	6/25, (24%)	3/25, (12%)	7/25, (28%)	9/25, (36%)	19/25, (76%)	3/25, (12%)	11/25, (44%)
ARDS	2/2, (100%)	0/2, (0%)	0/2, (0%)	0/2, (0%)	2/2, (100%)	0/2, (0%)	0/2, (0%)	0/2, (0%)	0/2, (0%)	0/2, (0%)	1/2, (50%)	0/2, (0%)	0/2, (0%)	0/2, (0%)	0/2, (0%)	0/2, (0%)	2/2, (100%)	2/2, (100%)	0/2, (0%)	0/2, (0%)	2/2, (100%)
Sepsis	4/4, (100%)	4/4, (100%)	0/4, (0%)	4/4, (100%)	2/4, (50%)	0/4, (0%)	0/4, (0%)	0/4, (0%)	2/4, (50%)	0/4, (0%)	1/4, (25%)	0/4, (0%)	3/4, (75%)	2/4, (50%)	0/4, (0%)	0/4, (0%)	4/4, (100%)	4/4, (100%)	0/4, (0%)	0/4, (0%)	4/4, (100%)
CRS	4/4, (100%)	1/4, (25%)	4/4, (100%)	2/4, (50%)	1/4, (25%)	2/4, (50%)	0/4, (0%)	0/4, (0%)	0/4, (0%)	3/4, (75%)	2/4, (50%)	1/4, (25%)	0/4, (0%)	0/4, (0%)	0/4, (0%)	0/4, (0%)	1/4, (25%)	1/4, (25%)	0/4, (0%)	0/4, (0%)	0/4, (0%)

**Abbreviations: IL = interleukin, TNFa = tumor necrosis factor alpha, IFNy = interferon gamma, sIL-2R = soluble IL-2 receptor, CRP = c-reactive protein, LDH = lactate dehydrogenase, PCT = procalcitonin, ESR = erythrocyte sedimentation rate, tBili = total bilirubin, Abs. Lymph. = absolute lymphocyte count, % lymph = lymphocyte differential.*

Supplemental Table 9: pooled estimates of all secondary cytokines and biomarkers of interest in all COVID-19 and comparison syndromes

	COVID-19	Hypo-inflam. ARDS	Hyper-inflam. ARDS	Sepsis	CRS
TNFa (pg/mL) *mean (CI)*	5 (2.3-10.7)	-	-	34.6 (20-59.9)	52.2 (2-1390.3)
diff (CI), p	**ref**			**29.6 (6.6-82.6), p = 0.0011**	**47.2 (3.9-2,072), p = 0.2815**
IL-1b (pg/mL) *mean (CI)*	4.4 (-9.1-17.9)	-	-	6.1 (-1.2-13.4)	-
diff (CI), p	**ref**			1.7 (-13.7-17), p = 0.7494	
IL-8 (pg/mL) *mean (CI)*	21.9 (4.5-107.6)	31.5 (11.4-87)	196 (57.8-665.2)	227.9 (96.3-539.3)	574.9 (9.4-35,310.3)
diff (CI), p	**ref**	**9.6 (-167.6-375.4), p = 0.952**	**174.1 (-13.9-2,736.3), p = 0.0987**	**206.0 (-1.7-2,445.9), p = 0.0561**	**553.0 (-283.1-200,676.4), p = 0.2786**
Ferritin (ng/mL) *mean (CI)*	1107.8 (736.5-1666.2)	-	-	-	6,8640.2 (30550.6-154219)
diff (CI), p	**ref**				**67,532.4 (26,614.7-169,786.5), p < 0.0001**
d-dimer (µg/mL) *mean (CI)*	8.3 (2.1-14.6)	-	-	2.4 (-3-7.9)	-
diff (CI), p	**ref**			**-5.9 (-14.2-2.4), p = 0.1483**	
CRP (µg/mL) *mean (CI)*	76.9 (51.1-102.7)	20.5 (0-77.0)	20.5 (0-77.0)	123.3 (79.8-166.8)	162.7 (62-263.4)
diff (CI), p	**ref**	**-56.4 (-137.8-25.1), p=0.2430**	**-53.3 (-144.3-37.7), p=0.3842**	**46.5 (-12.1-105.1), p = 0.1304**	**85.9 (-34.6-206.3), p = 0.1838**
LDH (U/L) *mean (CI)*	535 (427.2-642.7)	-	-	-	2,676 (2,130.8-3,221.2)
diff (CI), p	**ref**				**2,141 (1,585.3-2,696.8), p < 0.0001**
ESR (mm/hr) *mean (CI)*	46.8 (35.4-58.1)	-	-	-	-
diff (CI), p	**ref**				
PCT (ng/mL) *mean (CI)*	0.6 (-5.1-6.3)	-	-	18.2 (11.2-25.3)	-
diff (CI), p	**ref**			**17.6 (8.5-26.7), p = 0.0008**	
Albumin *mean (CI)*	3.1 (2.5-3.7)	2.3 (1.7-2.9)	2 (1.3-2.7)	2.6 (2.2-2.9)	2.1 (-0.1-4.3)
diff (CI), p	**ref**	**-0.8 (-1.9-0.3), p = 0.0602**	**-1.1 (-2.3-0.1), p = 0.0234**	**-0.5 (-1.4-0.4), p = 0.1478**	**-1 (-3.9-1.9), p = 0.3528**
IFNy (pg/mL) *mean (CI)*	10.8 (3.8-30.6)	-	-	-	3,722.1 (890.6-15,555.2)
diff (CI), p	**ref**				**3,711.3 (623.6-19,811.9), p < 0.0001**
IL-2 (pg/mL) *mean (CI)*	3.3 (2.1-4.5)	-	-	-	-
diff (CI), p	**ref**				
sIL-2R (pg/mL) *mean(CI)*	506.3 (153-1675.3)	-	-	-	12,396.0 (1,060.1-14,4953.2)
diff (CI), p	**ref**				**11,889.7 (298.4-19,0579.2), p = 0.0315**
IL-4 (pg/mL) *mean (CI)*	5.4 (4.5-6.3)	-	-	-	-
diff (CI), p	**ref**				
IL-10 (pg/mL) *mean (CI)*	47.5 (47.9-48.4)	-	-	368.1 (369.1-370.1)	759.4 (760.8-762.1)
diff (CI), p	**ref**			**300.2 (299.6-300.9), p < 0.0001**	**688.7 (687.5-689.9), p = 0.0001**
Abs. Lymph. *mean (CI)*	0.8 (0.5-1)	-	-	-	-
diff (CI), p	**ref**				
Lymph % (/mL) *mean (CI)*	14.3 (13.2-15.5)	-	-	-	-
diff (CI), p	**ref**				
Platelet *mean (CI)*	153.8 (153.3-154.2)	196.5 (195.7-197.3)	117.2 (116.4-118.1)	181.5 (180.6-182.4)	-
diff (CI), p	**ref**	**42.7 (42.1-43.3), p < 0.0001**	**-36.5 (-37.2-(-)35.8), p < 0.0001**	**27.8 (27.1-28.5), p < 0.0001**	
tBili (mg/dL) *mean (CI)*	0.9 (0.6-1.1)	1.2 (0.9-1.5)	2.2 (1.9-2.6)	0.8 (0.6-1)	4 (2.9-5.1)
diff (CI), p	**ref**	**0.3 (-0.2-0.8), p = 0.3296**	**1.4 (0.8-1.9), p < 0.0001**	**-0.1 (-0.5-0.3), p = 0.9804**	**3.1 (1.7-4.6), p = 0.0002**

All p-values and confidence-intervals are corrected for multiple comparisons.

**Abbreviations: COVID = coronavirus disease 19, hypo-ARDS = hypoinflammatory acute respiratory distress syndrome, hyper-ARDS = hyperinflammatory acute respiratory distress syndrome, CAR T = chimeric antigen receptor T cell, CRS = cytokine release syndrome, TNFa = tumor necrosis factor alpha, IL = interleukin, CRP = c-reactive protein, LDH = lactate dehydrogenase, ESR = erythrocyte sedimentation rate, PCT = procalcitonin, IFNy = interferon gamma, Abs. Lymph = absolute lymphocyte count, Lymph. % = lymphocyte differential, tBili = total bilirubin*

Supplemental Table 10: IL-6 in severe and critical subgroups of COVID-19 and comparison syndromes

	sqrt(N)-weighted analysis (primary)			*Inverse-variance weighted analysis*		
	Mean *pg/mL (95%CI)*	**Difference vs. Critical COVID-19 (95%CI)**	**p**	**Mean *pg/mL (95%CI)***	**Difference vs. Critical COVID-19 (95%CI)**	**p**
Severe COVID-19	37.3 (17.2-80.9)	**-16.2** **(-42.7-108.8)**	0.9418	34.7 (18.6-64.5)	**1.7** **(-23.4-93.9)**	1.0000
Critical COVID-19	55.3 (20.7-119.5)	***ref***	*ref*	32.9 (15.3-70.7)	***ref***	*ref*
Hypo-ARDS	198.6 (78.8-500.5)	**129.0** **(-16.6-915.2)**	0.1899	193.7 (71.3-526.5)	**160.8** **(4.0-983.0)**	0.0322
Hyper-ARDS	1,558.2 (511.6-4745.9)	**1,352.5** **(166.3-9052.4)**	0.0002	1558.3 (372.4-6520.1)	**1,525.3** **(151.0-13167.4)**	0.0002
Sepsis	983.6 (542.1-1784.4)	**835.38** **(165.8-3584.8)**	<0.0001	796.1 (377.8-1677.6)	**763.2** **(162.3-3213.7)**	<0.0001
CAR T CRS	3,110.5 (600.87-16102.5)	**2749.5** **(192.8-32250.5)**	0.0006	859.6 (146.1-5,055.9)	**826.7** **(34.8-10878.4)**	0.0075
Model Fit			***R^2 = 0.63***			***R^2 = 0.64***

All p-values and confidence-intervals are corrected for multiple comparisons.

**Abbreviations: sqrt(N) = square root of sample size, COVID-19 = coronavirus disease 19, hypo-ARDS = hypoinflammatory acute respiratory distress syndrome, hyper-ARDS = hyperinflammatory acute respiratory distress syndrome, CAR T = chimeric antigen receptor T cell, CRS = cytokine release syndrome*

Supplemental Table 11: pooled estimates of all secondary cytokines and biomarkers of interest in severe & critical COVID-19 and comparison syndromes

	Severe COVID-19 *mean (95% CI)*	Critical COVID-19 *mean (95% CI)*	Hypo-inflammatory ARDS *mean (95% CI)*	Hyper-inflammatory ARDS *mean (95% CI)*	Sepsis *mean (95% CI)*	CRS *mean (95% CI)*
TNFa (pg/mL) *mean (CI)*	3.8 (1.4-10.7)	50.2 (3.1-809.9)	-	-	34.6 (19.1-62.8)	52.2 (1.5-1836.7)
diff (CI), p	**-46.4 (-50.1-79.2), p = 0.1573**	**ref**			**-15.6 (-49.1-963.0), p = 0.9662**	**2.0 (-50.0-11102.0), p = 1.0000**
IL-1b (pg/mL) *mean (CI)*	5 (0-28.8)	1 (0-57.7)	-	-	6.1 (0-18)	-
diff (CI), p	**4 (-65.9-73.9), p = 0.9069**	**ref**			**5.1 (-60.7-70.9), p = 0.8505**	
IL-8 (pg/mL) *mean (CI)*	21.4 (2.7-171.7)	25 (0.2-3595.1)	31.5 (9.3-107.2)	196 (44.9-856.1)	227.9 (80.6-644.4)	574.9 (4.0-82,672)
diff (CI), p	**-3.6 (-27703.1-19484.6), p = 0.9999**	**ref**	**6.5 (-13,300-20,369.2), p = 0.9994**	**168 (-2306.3-137596.3), p = 0.5662**	**202.9 (-1,725.8-13,9717.7), p = 0.5106**	**549.9 (-8279.9-4215922.6), p = 0.4956**
Ferritin (ng/mL) *mean (CI)*	974.6 (495.1-1918.3)	1283.9 (560-2943.7)	-	-	-	68,640.2 (27,003.1-174,479.5)
diff (CI), p	**-309.3 (-1003.3-3381.3), p = 0.7737**	**ref**				**67,356.3 (14,798.8-292,734.4), p = 0.0002**
d-dimer (µg/mL) *mean (CI)*	3.3 (0.0-11.3)	16.5 (7.9-25.2)	-	-	2.4 (0.0-7.2)	-
diff (CI), p	**-13.2 (-26.6-0.17), p = 0.0528**	**ref**			**-14.1 (-25.3-(-)2.9), p = 0.0159**	
CRP (µg/mL) *mean (CI)*	55.9 (23.1-88.8)	102.5 (56.8-148.2)	20.5 (0-77.2)	23.6 (0-82.4)	123.3 (79.7-166.9)	162.7 (61.7-263.7)
diff (CI), p	**-50.8 (-121.9-28.7), p = 0.3274**	**ref**	**-92.7(-179.6-15.5), p=0.1150**	**-89.6 (-185.0-27.1), p=0.1854**	**15.6 (-63.8-105.4), p = 0.9361**	**55 (-88.2-208.6), p = 0.6944**
LDH (U/L) *mean (CI)*	416.3 (266.7-565.8)	668.4 (529.0-807.8)	-	-	-	2676 (2205.9-3146.1)
diff (CI), p	**-252.1 (-489.2-(-)14.9), p = 0.0571**	**ref**				**2,007.63 (1438.9-22576.4), p < 0.0001**
ESR (mm/hr) *mean (CI)*	44.4 (30.4-58.5)	-	-	-	-	-
diff (CI), p	**N/A**					
PCT (ng/mL) *mean (CI)*	0.2 (0.0-8.2)	1.2 (0.0-10.9)	-	-	18.2 (10.9-25.5)	-
diff (CI), p	**-1 (-14.6-12.5), p = 0.9741**	**ref**			**17 (4-30), p = 0.0113**	
Albumin *mean (CI)*	3.5 (1.7-5.2)	3.0 (2.0-3.9)	2.3 (1.7-2.9)	2.0 (1.2-2.8)	2.6 (2.2-3)	2.1 (0.0-4.5)
diff (CI), p	**0.4 (-2.2-3.2), p = 0.9699**	**ref**	**-0.7 (-2.2-0.9), p = 0.5649**	**-1.0 (-2.6-0.7), p = 0.3162**	**-0.5 (-1.8-1.0), p = 0.8561**	**-0.9 (-4.4-2.6), p = 0.8938**
IFNy (pg/mL) *mean (CI)*	6.1 (1.6-23.0)	41.0 (10.0-168.1)	-	-	-	3,722.1 (894-15497.7)
diff (CI), p	**-34.9 (-40.4-15.8), p = 0.0931**	**ref**				**3681.1 (328.4-37462.0), p = 0.0010**
IL-2 (pg/mL) *mean (CI)*	2.3 (0.4-4.2)	5.6 (2.3-8.9)	-	-	-	-
diff (CI), p	**-3.3 (-7.2-0.5), p = 0.0762**	**ref**				
sIL-2R (pg/mL) *mean(CI)*	592.0 (138.2-2536.1)	152.0 (13.2-1748.0)	-	-	-	123956 (744.4-206428)
diff (CI), p	**440.0 (-132.8-18099.8), p = 0.3404**	**ref**				**12244.2 (-13.2-1107279.4), p = 0.0527**
IL-4 (pg/mL) *mean (CI)*	4.3 (2.8-5.8)	7.1 (5.3-8.2)	-	-	-	-
diff (CI), p	**-2.8 (-3.9-(-)1.8), p = 0.0006**	**ref**				
IL-10 (pg/mL) *mean (CI)*	43.9 (43.5-44.3)	70.9 (70.2-71.6)	-	-	355.7 (354.7-356.7)	745.3 (743.9-746.6)
diff (CI), p	**-27.0 (-27.6-(-)26.4)), p < 0.0001**	**ref**			**284.1 (284.1-285.5), p < 0.0001**	**674.4 (673.3-675.5), p = < 0.0001**
Abs. Lymph. *mean (CI)*	0.9 (0.6-1.1)	0.6 (0.3-1.0)	-	-	-	-
diff (CI), p	**0.2 (-0.2-0.6), p = 0.2567**	**ref**				
Platelet (/mL) *mean (CI)*	147.5 (146.7-148.3)	130 (129.5-130.6)	174.12 (173.2-175.1)	94.0 (93.0-95.0)	155.2 (154.1-156.3)	-
diff (CI), p	**17.5 (16.7-18.2), p = <.0001**	**ref**	**44.1 (43.3-44.9), p = <.0001**	**-36 (-36.8--35.2), p = <.0001**	**25.2 (24.3-26.1), p = <.0001**	
Lymph. % *mean (CI)*	14.2 (10.8-17.6)	10.1 (1.0-19.2)	-	-	-	-
diff (CI), p	**4.2 (-4.1-12.4), p = 0.0983**	**ref**				
tBili (mg/dL) *mean (CI)*	0.7 (0.1-1.3)	1.0 (0.6-1.3)	1.2 (0.9-1.5)	2.2 (1.9-2.6)	0.8 (0.6-1)	4.0 (2.9-5.1)
diff (CI), p	**-0.3 (-1.2-0.6), p = 0.8726**	**ref**	**0.2 (-0.4-0.8), p = 0.7447**	**1.3 (0.6-1.9), p = 0.0005**	**-0.1 (-0.7-0.4), p = 0.876**	**3.0 (1.5-4.6), p = 0.0005**

All p-values and confidence-intervals are corrected for multiple comparisons.

**Abbreviations: COVID = coronavirus disease 19, hypo-ARDS = hypo-inflammatory acute respiratory distress syndrome, hyper-ARDS = hyperinflammatory acute respiratory distress syndrome, CAR T = chimeric antigen receptor T cell, CRS = cytokine release syndrome, TNFα = tumor necrosis factor alpha, IL = interleukin, CRP = c-reactive protein, LDH = lactate dehydrogenase, ESR = erythrocyte sedimentation rate, PCT = procalcitonin, IFNɣ = interferon gamma, Abs. Lymph = absolute lymphocyte count, Lymph. % = lymphocyte differential, tBili = total bilirubin*

Supplemental Table 12: Timing of IL-6 measurement in included COVID-19 studies

Study	Time of IL-6 measurement	Mean IL-6 (SD) *pg/mL*
Chen G. et al.	On admission	**60.2 (66.2)**
Gritti et al.	On admission	**158.7 (34.1)**
Qin C. et al.	On admission	**29.7 (33.3)**
Wan S. et al.	On admission	**37.8 (7.8)**
Wang Z. et al.	On admission	**82.6 (94.3)**
Wu C. et al.	On admission	**8 (3.9)**
Zhang B. et al. ***(group 1)***	On admission	**44.1 (64.7)**
(group 2)		**6.5 (1.3)**
(group 3)		**31.5 (27)**
(group 4)		**10.4 (6.7)**
Zhou F. et al.	On admission	**11 (5.1)**
Shi Y. et al.	On entry into study	**200 (300)**
Huang C. et al.	Median 4 (IQR 2-5) days following transfer to participating center	**16.7 (29.6)**
Cai Q. et al.	Peak during hospitalization	**38.8 (38.1)**
Herold et al.	Peak between admission and intubation	**176.8 (123.2)**
Yang Y. et al. ***(severe)***	Peak during study	**31.5 (8.9)**
(critical)		**37.7 (22.1)**
Liu J. et al.	Peak during 16 days post disease-onset	**70 (20)**
Chen J et al.	Within 48h of death	**81.3 (143.9)**
Zhang, B. et al. ***(critical)***	Within 24 hours of death	**208.7 (116.1)**
Gao Y. et al.	Unspecified	**39.4 (26.8)**
Huang Y. et al.	Unspecified	**357.2 (643)**
Ruan Q. et al.	Unspecified	**11.4 (8.5)**
Xu Y. et al.	Unspecified	**22.5 (28)**
Chen X. et al. ***(severe)***	Unspecified time following admission	**8.6 (10.2)**
(critical)		**62.7 (63.9)**
Diao B. et al.	Unspecified time following admission	**192.8 (276.8)**
Fu S. et al.	Unspecified time following admission	**13.3 (29.5)**
Zhang H. et al.	Unspecified time following admission	**21.7 (32.5)**
Liu T. et al.	"After treatment"	**36 (5)**

Supplemental Table 13: sensitivity analyses of peak IL-6 in COVID-19 vs. comparator disorders

	All COVID			***Severe and Critical COVID subgroups***		
	Mean *pg/mL (95%CI)*	**Difference vs. Critical COVID-19 (95%CI)**	**p**	**Mean *pg/mL (95%CI)***	**Difference vs. Critical COVID-19 (95%CI)**	**p**
All COVID-19	61.3 (15.1-248.3)	***ref***	***ref***	-	**-**	-
Severe COVID-19	-	**-**	-	41.48 (4.0-428.3)	**-43.0** **(-90.1 – 2258.5)**	0.9817
Critical COVID-19	-	**-**	-	78.1 (12.4-428.3)	***ref***	***ref***
Hypo-ARDS	198.6 (61.1-645.9)	**148.2** **(-45.3 - 2,136.9)**	0.4656	198.6 (58.7-672.2)	**141.2** **(-78.5 – 4060.6)**	0.8003
Hyper-ARDS	1,558.2 (376.3-6,452.6)	**1,615.7** **(66.6 – 21240.4)**	0.0116	1,558.2 (358.6-6771.1)	**1,734.2** **(-7.1 - 39371.9)**	0.0572
Sepsis	983.6 (460.0-2,103.0)	**995.5** **(73.7 - 7995.0)**	0.0070	983.6 (448.3-2,157.9)	**933.5** **(-7.0 – 15619.9)**	0.0585
CAR T CRS	3,110.5 (381.8-25341.9)	**3,291.3** **(69.3 - 83172.9)**	0.0153	3,110.5 (355.6-27209.8)	**3553.1** **(-2.4 – 149005.0)**	0.0519
Model Fit			***R^2 = 0.60***			***R^2 = 0.61***

Note: While all COVID-19 studies in this sensitivity analysis report a peak IL-6, all ARDS and sepsis studies report an enrollment IL-6.

All p-values and confidence-intervals are corrected for multiple comparisons.

**Abbreviations: COVID-19 = coronavirus disease 19, hypo-ARDS = hypo-inflammatory acute respiratory distress syndrome, hyper-ARDS = hyperinflammatory acute respiratory distress syndrome, CAR T = chimeric antigen receptor T cell, CRS = cytokine release syndrome*

REFERENCES

1. World-Health-Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. In: World Health Organization; 2020.
2. National-Health-Commission-of-China. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia. In: China NHCo, ed2020.
3. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307(23):2526-2533.
4. Sinha P, Delucchi KL, Thompson BT, et al. Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study. *Intensive Care Med.* 2018;44(11):1859-1869.
5. Sinha P, Delucchi KL, McAuley DF, O'Kane CM, Matthay MA, Calfee CS. Development and validation of parsimonious algorithms to classify acute respiratory distress syndrome phenotypes: a secondary analysis of randomised controlled trials. *Lancet Respir Med.* 2020;8(3):247-257.
6. Wilson JG, Calfee CS. ARDS Subphenotypes: Understanding a Heterogeneous Syndrome. *Critical Care.* 2020;24(1):102.
7. Seymour CW, Kennedy JN, Wang S, et al. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA.* 2019;321(20):2003-2017.
8. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.
9. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. *Blood.* 2017;130(21):2295-2306.
10. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014;371(16):1507-1517.
11. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med.* 2018;378(5):439-448.
12. Turtle CJ, Hay KA, Hanafi LA, et al. Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor-Modified T Cells After Failure of Ibrutinib. *J Clin Oncol.* 2017;35(26):3010-3020.
13. Tricco AC, Antony J, Zarin W, et al. A scoping review of rapid review methods. *BMC Medicine.* 2015;13(1):224.
14. Haby MM, Chapman E, Clark R, Barreto J, Reveiz L, Lavis JN. What are the best methodologies for rapid reviews of the research evidence for evidence-informed decision making in health policy and practice: a rapid review. *Health Research Policy and Systems.* 2016;14(1):83.
15. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology.* 2014;14(1):135.
16. Higgins JT, J, Chandler J, Cumpston M, Li T, Page M, Welch V. *Cochrane Handbook for Systematic Reviews of Interventions. (version 6.0).* 2019.
17. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis.* 1 ed. New York: Springer-Verlag; 2001.